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(54) Title: METHOD FOR THE PRODUCTION OF COPOLYMERS OF LACTIDE AND ε-CAPROLACTONE AND ARTICLES THEREOF FOR MEDICAL APPLICATIONS

(57) Abstract

The invention relates to a method for the production of an article from a copolymer of lactide and ε-caprolactone for medical applications, in which method the copolymer is obtained by a synthesis which is carried out as a bulk synthesis at a temperature of 80 to 160 °C. Articles according to the invention can be used in numerous fields, but are in particular advantageous if they are employed in biomedical fields. Examples are an implant for the repair of a meniscus or a blood vessel, stents or artificial skin. Stents are small spirals which are used to hold open (coronary) arteries which have silted up. Use in abdominal wall reconstruction is also possible.

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Method for the production of copolymers of lactide and E-Caprolactone and articles thereof for medical applications.

The invention relates to a method for the production of an article from a copolymer of lactide and ε-caprolactone for medical applications.

Background of the Invention

A method of this type is disclosed in JP-58-122643. In this publication it is described that films and sheets which can be used as anti-adhesive material can be made from a lactide/ε-caprolactone copolymer. During an operation, the sheet or film is inserted between organs or tissues which must not grow together post-operatively. To this end, copolymers are synthesized from monomers which are polymerized in a weight ratio of 25 to 75 parts of lactide to 75 to 25 parts of ε-caprolactone in the presence of tin octoate at a temperature of 160°C.

In surgery there is a need in certain applications for materials which are biocompatible and biodegradable, without toxic substances being released during degradation, but where the materials also have a high tensile strength and elasticity. The material as described in JP-A-58-122643 is unsuitable for a number of applications because this material does not have the desired tensile strength and elasticity.

In US 4,057,537 it is described how copolymers of L-(-)-lactide and ε-caprolactone are synthesized at a

temperature above the melting point of the lactide. According to US 4,057,537, a lower polymerization temperature can be chosen, but then only in a suspension or solution in an inert medium. This lower temperature is regarded as unfavourable and is alleged to yield less desired polymers. It is not described in US 4,057,537 that the copolymers can be used in medical applications.

Summary of the Invention

The aim of the invention is to provide a method which yields a copolymer which has a higher tensile strength than was known in the prior art and which is suitable for the production of materials for flexible implants such as meniscus, artificial skin or an artificial blood vessel.

According to the invention this is achieved in that the copolymer is obtained by a synthesis which is carried out as a bulk synthesis at a temperature of 80 to 160°C.

More specifically, this invention is a method for the production of an article from the copolymer of lactide and ε-caprolactone for medical applications, comprising:

- purifying the lactide and the ε-caprolactone,
- introducing the purified lactide and the purified ε-caprolactone into a vessel and, allowing the purified lactide and purified caprolactone to react by bulk synthesis at a temperature from about 80°C to below about 160°C to form a copolymer,
- shaping the copolymer into an article.

By this means it is surprisingly possible to obtain a copolymer having a molecular weight of from 500,000 to 1,000,000 which combines a tensile strength of at least 34 MPa with a high elongation at break.

Preferably, the synthesis is carried out at 80 to 110°C and more preferentially the synthesis is carried out at a temperature below the melting point of lactide, that is to say at a temperature below 98°C.

By the term "bulk synthesis" herein is meant a synthesis in which the reaction medium does not contain solvents and which also does not take place in a suspension or emulsion.

An article can be produced from the copolymer in any known way. Known methods comprise injection molding, hot forming, cutting, milling, sawing and also synthesis in a mold having virtually the shape which the article must acquire.

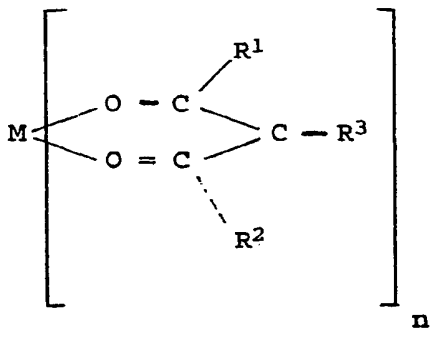
According to the invention, the lactide and the ε-caprolactone can be added in any desired weight ratio and are preferably added in a weight ratio of 10:90 to 99.1:0.1 and more preferentially in a ratio of 45:55 to 55:45.

If copolymers are made with small amounts of ε-caprolactone, for example 2 to 5 mol-%, the result is a material which has a high modulus, tensile strength and impact strength. It can then, for example, be used for the production of bone plates and screws.

In general, the synthesis is carried out in the presence of a catalyst. The catalyst can be chosen from all catalysts suitable for lactones and carbonates, as are known from the

technology to those skilled in the art. Examples of such catalysts are the catalysts as described in U.S. 4,539,981, hereby incorporated by reference, that is to say tin octoate, antimony trifluoride, zinc powder, dibutyltin oxide and tin oxalate.

A preferred catalyst consists of a compound according to Formula I:



(I)

in which M is a metal ion and n is a number from 1 to 4 and equal to the valency of the metal ion and in which the groups R^1 and R^2 independently of independently of one another are an alkyl, aryl or cycloaliphatic group and R^3 is an alkyl, aryl or cycloaliphatic group or a hydrogen atom. It is further possible that the alkyl, aryl or cycloaliphatic groups which form part of R^1, R^2 or R^3 are substituted by halogens.

More preferentially, a catalyst such as described in Formula I is used in which M is a Zn^{2+} and R^1 is a tertiary butyl group and R^2 is an ethyl group and R^3 is an H, in which

case the compound has the name bis-(2,2-dimethyl-3,5-heptanedionato-O,O')-zinc, or where M is an Sn^{2+} and R^1 and R^2 are a methyl and R^3 is an H, in which case the compound has the name bis-(2,4-pentanedionato-O,O')-tin(II).

Tin octoate is a catalyst of secondary preference.

The catalyst is present in an amount of 10^{-7} to 10^{-3} and preferably approximately 10^{-5} mol/mol relative to the monomers.

The synthesis is preferably continued until less than 0.1% by weight of residual monomer remains in the reaction mixture. In general, this will be a period of from 100 to 400 hours. The polymerization time required depends on the polymerization temperature. In addition, the time is dependent on the concentration of the catalyst.

The lactide can be chosen from L-lactide, D-lactide, DL-lactide and mixtures hereof.

The lactide and ε-caprolactone monomers are preferably purified before use to remove contaminants. In the case of lactide, for example, purification is possible by recrystallisation from toluene dried over sodium. ε-Caprolactone can be purified, for example, by distillation under a reduced N_2 atmosphere from CaH_2.

Preferably, the two monomers are purified until their contamination by impurity containing hydroxyl groups is less than 1 ppm.

In a further embodiment of this invention, additional other monomers can be added to the reaction mixture in amounts of from none up to a percentage by weight of 50%. These

monomers are preferably chosen from other lactones, such as glycolide, dioxanone, 1,4-dioxane-2,3-dione, β-propiolactone, tetramethylglycolide, β-butyrolactone, γ-butyrolactone or pivalolactone, or cyclic carbonates such as trimethylene carbonate, 2,2-dimethyl-trimethylene carbonate and the like.

The lactones can consist of the optically pure isomers or of two or more optically different isomers.

Furthermore, in another embodiment of this invention, comonomers based on hydroxy-carboxylic acids can be incorporated. Incorporation is possible, for example, amounts of from none a percentage by weight of 50%, but is preferably not higher than about 10%. Said comonomers can be chosen, for example, from the group consisting of

α-hydroxybutyric acid,
α-hydroxyisobutyric acid,
α-hydroxyvaleric acid,
α-hydroxyisovaleric acid,
α-hydroxycaproic acid,
α-hydroxyisocaproic acid,
α-hydroxy-α-ethylbutyric acid,
α-hydroxy-β-methylvaleric acid,
α-hydroxyheptanoic acid,
α-hydroxyoctanoic acid,
α-hydroxydecanoic acid,
α-hydroxymyristic acid,
α-hydroxystearic acid or combinations thereof.

The resulting material can be reinforced by mixing fibrous material into the reaction mixture or by combining the resulting material, by melting or otherwise, with fibrous reinforcing material. The fibrous material can be chosen from all possible biocompatible fibers and is preferably chosen from the highly oriented, strong and rigid fibers. The fibers may or may not be biodegradable. Examples are polylactide fibers, polyglycolide fibers, fibers of lactide/glycolide copolymers and fibers of copolymers of lactide and trimethylene carbonate. The fibrous material can be present in the form of loose fibers, mats, woven fabrics, knitted fabrics or otherwise.

The conventional fillers, inhibitors, release agents, etc. can also be added to the mixture.

Articles according to the invention have numerous uses, but are in particular advantageous if they are employed in biomedical fields. Examples are an implant for the repair of a meniscus or a blood vessel, stents or artificial skin. Stents are small spirals which are used to hold open (coronary) arteries which have deposits on inner walls. Use in abdominal wall reconstruction is also possible.

It is also possible to make nerve guides from the copolymers. A nerve guide is a small tube which can be used to enable a nerve branch which has been broken by a fracture or otherwise to grow together again through the tube, after which the tube degrades.

Description of Preferred Embodiments

The invention will be illustrated with the aid of the following examples, without being restricted thereto.

The intrinsic viscosity was measured in chloroform at 25°C using an Ubbelohde viscometer.

Monomer conversion and copolymer composition were determined using 'H NMR at 300 MHz in solutions in deuterated chloroform.

The average length of the monomer sequences was determined using '3C NMR at 75 MHz.

Thermal properties were determined using a Perkin Elmer DSC-7, 5-10 mg samples being heated at a rate of 20°C per minute.

The stress-strain behaviour was determined on an Instron 4301 tensile tester, 4 x 50 x 1 mm samples cut from 3 by 10 by 0.1 cm plates obtained by compression molding at room temperature being measured at a crosshead speed of 10 mm/min. The yield strength (that is to say the yield stress), the elongation at break and the ultimate tensile strength were determined from these measurements.

Dynamic thermal analysis was carried out on a Rheometrics RSA-II DMTA. In the tension mode under a constant load of 50 g, the 4 x 50 x 1 mm samples obtained by compression molding and cutting were exposed to an oscillating strain with a maximum amplitude of 0.5% at a frequency of 1 Hz. The heating rate was 5°C/min.

Example I

L-Lactide (CCA, The Netherlands) was purified by recrystallisation from toluene dried over sodium. ε-Caprolactone (Janssen Chemica, Belgium) was purified by drying over CaH_2 and distilling under reduced pressure in a nitrogen atmosphere. The monomers were introduced, in a ratio of 50:50 mol/mol into silanised glass ampoules which had been placed under vaccuum and into which tin octoate (Sigma Corp., USA) was also added in an amount of 1×10^{-5} mol of catalyst per mol of monomer.

The reaction was carried out for 60 days at a temperature of 80°C.

As a consequence of the difference in reactivity between L-lactide and ε-caprolactone, the lactide first reacted preferentially and only then the ε-caprolactone. This results in copolymers which have a block-like structure and have an average sequence length of 11.0 for the L-lactide and 5.5 for the ε-caprolactone. The intrinsic viscosity was 11.5 dl/g.

Example II

The method of Example I was followed at a reaction temperature of 110°C. Virtually complete conversion (to a percentage by weight of less than 2% residual monomer) was achieved after 10 days, after which the reaction was stopped. Copolymers having a block structure were formed, which had an average sequence length of 8.5 for the L-lactide and 3.7 for the ε-caprolactone. The intrinsic viscosity was 9.9 dl/g.

Probably the sequence length at 110°C is shorter than at 80°C because of a higher degree of transesterification during the raction. The fact that the difference in reactivity between L-lactide and ε-caprolactone is less pronounced at higher temperatures may also play a role. A longer sequence length is related to a higher crystallinity and thus to a higher rigidity. As a consequence, the polymer material in Example I is more rigid than the polymer material in Example II, while the material in Example II is tougher than the material in Example I.

Example III

The method of Example I was followed at a reaction temperature of 120°C for 5 days until the residual monomer content was less than 2% by weight. Copolymers having a block structure were formed, which had an average sequence length of 5.5 for the L-lactide and 2.5 for the ε-caprolactone. The intrinsic viscosity was 7.8 dl/g.

Example IV

The method of Example I was followed at a reaction temperature of 160°C for 2 days until the residual monomer content was less than 2% by weight. Copolymers having a block structure were formed, which had an average sequence length of 3.9 for the L-lactide and 2.1 for the ε-caprolactone. The intrinsic viscosity was 3.4 dl/g.

It can be concluded from the sequence lengths of the blocks in the polymers in Examples I to IV that the chain becomes more block-like when the reaction temperature is

lowered. The mechanical properties, and specifically the tensile strength, become better as a result. The mechanical properties of the polymer from Example II are comparable with the properties of, for example, Estane®, a type of polyurethane used in biomedical application.

Example V

The reaction product from Example I was processed by compression molding at 200°C, followed by slow cooling and annealing for 8 hours at 100°C, to give 3 by 10 by 0.1 cm plates.

Example VI

The reaction product from Example II was processed in the manner described in Example V to give measuring rods.

Example VII

Using a DSC scan, a T_g of -39°C was determined for the measuring rods from Example V, which indicates an amorphous phase rich in ε-caprolactone. The material also had two melt endotherms: one at 44.3°C with a ΔH of 5.8 J/g and one at 149°C, with a ΔH of 14.8 J/g. This indicates two crystalline phases: a poly-ε-caprolactone phase and a poly-L-lactide phase. No indications for an amorphous L-lactide phase were found.

The stress-strain behaviour of the measuring rods was also measured. The results of these measurements are given in Table 1.

Example VIII

Using a DSC scan, a T_g at -15°C and a T_g at 55°C were measured for the measuring rods from Example VI, which

indicates two different amorphous phases. The second, which is rich in poly-L-lactide, displays an enthalpy recovery peak. The material had a melt endotherm T_m at 102°C with a ΔH of 4.0 J/g, which melt endotherm indicates the melting of small and imperfect L-lactide crystallites. The material was completely amorphous before processing and displayed some crystallinity only after annealing for 3 weeks at room temperature.

The stress-strain behaviour of the measuring rods was also measured. The results are given in Table 1.

Table 1: Results of the stress-strain measurements

	Example VII 80°C	Example VIII 110°C
Initial modulus (MPa)	84	5.2
Elongation at break (%)	480	880
Tensile strength (MPa)	5.0	1.0
Ultimate tensile strength (MPa)	18.2	9.0

It can be concluded from this that a lowering of the reaction temperature leads to copolymers with longer average sequence lengths of the respective comonomers, which leads to higher moduli and tensile strengths, while the elongation at break is lower. The maximum achievable molecular weight is higher.

While the invention has been described in connection with what is presently considered to be the most practical and preferred embodiments, the invention is not limited to the disclosed embodiments but, on the contrary, is intended to cover various modifications and equivalents included within the spirit and scope of the following claims.

CLAIMS

1. A method for the production of an article from the copolymer of lactide and ε-caprolactone for medical applications, comprising:

- purifying said lactide and said ε-caprolactone
- introducing said purified lactide and said purified ε-caprolactone into a vessel and
- allowing said purified lactide and said purified ε-caprolactone to react by bulk synthesis at a temperature of from about 80°C to below about 160°C to form said copolymer, then
- shaping said copolymer into said article.

2. The method according to claim 1, wherein the synthesis is carried out at 80-110°C.

3. The method according to claim 1, wherein the synthesis is carried out below the melting point of lactide.

4. The method according to claim 1, wherein the lactide and ε-caprolactone monomers are reacted with one another in a ratio of 10:90 to 99.9:0.1.

5. The method according to claim 4, wherein the lactide and ε-caprolactone monomers are reacted with one another in a ratio of 44:55 to 55:45.

6. The method according to claim 1, wherein purities containing hydroxyl groups of less than 1 ppm before use.

7. The method according to claim 1, whereby the synthesis is carried out in the presence of a catalyst, wherein the

catalyst is chosen from the group consisting of tin octoate, antimony trifluoride, zinc powder, dibutyltin oxide and tin oxalate, bis-(2,2-dimethyl-3,5-heptanedionato-O,O')-zinc and bis-(2,2-pentanedionato-O,O')-tin(II).

8. The method according to claim 7, wherein the catalyst is present in an amount of 10-7 to 10-3 mol/mol relative to the monomers.

9. The method according to claim 1, wherein the synthesis is continued until less than 0.1% by weight of residual monomer remains in the reaction mixture.

10. The method according to claim 1, wherein the copolymer is reinforced with fibers.

INTERNATIONAL SEARCH REPO[redacted]

International Application No PCT/NL 91/00164

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)°

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 08 G 63/08 C 08 G 63/80 A 61 L 27/00
A 61 L 31/00

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 08 G

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
X	WO,A,8404311 (HEXCELL CORP.) 8 November 1984, see claims 1-5,7,10-13,19,29; page 8, line 10 - page 14, line 14; examples 1-4,6	1,2,4,6 -8,10
A	---	3,9
X	US,A,4057537 (R.G. SINCLAIR) 8 November 1977, see column 2, line 40 - column 6, line 16; column 7, lines 6-17; examples 1,5 (cited in the application)	1,2,4-6 ,10
A	---	3,7-9
X	US,A,4045418 (R.G. SINCLAIR) 30 August 1977, see claims 1,4-7; column 4, line 1 - column 6, line 46; example 1	1,2,4,6
A	--- -/-	3,7-9

° Special categories of cited documents : [10]

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
16-12-1991	30. [illegible]
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	[illegible]

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
P,X	Polymer Bulletin, vol. 25, no. 3, March 1991, Springer Verlag (Berlin, DE) D.W. Grijpma et al.: "Polymerization temperature effects on the properties of L-lactide and epsilon-caprolactone copolymers", pages 335-341, see pages 335-338	1-8
A	EP,A,0108635 (JOHNSON & JOHNSON PRODUCTS) 16 May 1984, see page 1, lines 7-10; page 3, lines 9-18; page 6, line 28 - page 7, line 1 (cited in the application)	7-9

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. NL 9100164 SA 51633

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 20/01/92
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US-A- 4057537	08-11-77	None	
US-A- 4045418	30-08-77	None	
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